

Mechanisms for the Interaction of Dopamine and Norepinephrine in the Prefrontal Cortex: Implications for the Treatment of Cognitive Symptoms of Schizophrenia

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Reductions in prefrontal cortical dopamine (DA) levels have been associated with the cognitive symptoms of schizophrenia. When removal of the dopamine innervation to the prefrontal cortex (PFC) was tested in animal models, researchers reported a loss of dendritic spines. Anatomical arrangements in the PFC suggest that dopamine may play a role in the regulation of dendritic architecture. Atypical antipsychotics, but not typical antipsychotics, reverse the loss of dendritic spines seen upon DA denervation. Atypical antipsychotic drugs have also been reported to reduce cognitive symptoms of schizophrenia. Taken together with their ability to reverse spine loss, these data suggest that spine loss may be a pathological correlate to cognitive deficits associated with the prefrontal cortex. The mechanism by which these drugs act to restore DA tone in the PFC remains unclear. Recent data has suggested that norepinephrine (NE) terminals are capable of releasing the NE “precursor” DA. Atypical antipsychotic drugs have a wide target profile, including antagonism of NE autoreceptors. These data suggest that interactions between the DA and NE systems may play a role in treatment for schizophrenia. Although DA and NE have been implicated in disorders involving the prefrontal cortex such as schizophrenia, affective disorders, and attention-deficit hyperactivity disorder (ADHD), the mechanism for interactions between DA and NE has not been widely investigated. Understanding how these systems interact should have a major impact on therapeutic possibilities for disorders arising from disruption of PFC function.

Dopamine (DA) and norepinephrine (NE) have consistently been shown to play a crucial role in cognitive processes. DA and NE share a common synthetic pathway, and have both been implicated in psychiatric disorders such as attention-deficit hyperactivity disorder (ADHD)^{1,2}, affective disorders³, and schizophrenia⁴⁻⁶. Both transmitter systems send projections to the prefrontal cortex (PFC), where they have been shown to be involved in processes such as attention, working memory, executive function, and behavioral inhibition^{1, 2, 4, 7-14}. Disturbances in PFC function are linked to the cognitive symptoms of schizophrenia, and are thought to be a result of a hypodopaminergic state in the PFC¹⁵. First generation antipsychotics, such as haloperidol, primarily target the D₂ dopamine receptor¹⁶. These drugs tend to improve the positive symptoms of the disorder, such as hallucinations and delusions, yet have little effect on cognitive and negative symptoms¹⁷. Interestingly, second generation antipsychotics, such as clozapine, have a larger target profile and are more effective in treating the cognitive and negative symptoms of schizophrenia, such as

deficits in working memory and a flattened affect^{18, 19}. Among those receptors targeted by second-generation drugs are NE receptors, including α_{2C} -receptors, increasing interest in the possible interactions of these parallel pathways. Despite commonalities in synthesis, localization, and drug interactions, interactions between DA and NE systems within the prefrontal cortex remain poorly understood. Here we will review evidence for the role of DA and NE in aspects of cognition, then delve into recent studies that investigate possible interactions of these systems at the level of receptors, transporters, and possible co-release, and finally the implications that DA/NE interactions have for our understanding of neuropsychiatric disorders.

DOPAMINE AND NOREPINEPHRINE NEURONS PROJECT TO THE PFC

Early studies of both dopamine and norepinephrine focused on the localization of these transmitters in the brain. Using fluorescent histochemistry, as well as electron microscopy, these studies showed that both DA and NE are present in the prefrontal cortex²⁰⁻²².

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Prefrontal cortical DA projections originate from neurons in the ventral tegmental area (VTA)²³, while NE projections originate from the locus coeruleus (LC)²⁴. Dopamine has an abundance of axon terminals in deep layers of cortex in the rodent²⁰ and primate²⁵, primarily in layer V. This coincides well with the distribution of dopamine receptors of which D₁ is the dominant form in the PFC²⁶. This selective area of activation implies a selective function for the DA pathway in the PFC, which is further strengthened by the presence of specific synaptic contacts being made onto the shafts and spines of layer V pyramidal cells²⁵. Several studies suggest that NE terminals are more evenly distributed than DA terminals throughout the prefrontal cortex^{21, 27}. The diffuse nature of NE terminals across both rodent and primate PFC lamina suggests a more general role of this transmitter in the PFC. Norepinephrine terminals lack the synaptic contacts made by DA terminals. However, functional specificity of NE may be determined by NE receptors' laminar distribution. Norepinephrine and DA distribution in the PFC suggests these transmitters' involvement in PFC function.

DOPAMINE AND NOREPINEPHRINE RECEPTOR LOCALIZATION

Following these careful characterizations of dopamine and norepinephrine distribution, investigation began to shift from neurotransmitters to their receptors. Autoradiography was used in early studies, using tridiated ligands that showed specificity for the various dopamine and norepinephrine receptors²⁸⁻³⁰.

Currently, five dopamine receptors have been identified, which are classified as adenylate cyclase activating "D₁-like", or inhibiting "D₂-like" receptors, with D₁ and D₅ being grouped together and D_{2,4} grouped together³¹. Dopamine receptor identification in early studies made no distinction between the various subtypes, and suggested that DA receptor localization in the PFC was focused in the deep layers V and VI²⁹. D₂ receptors are localized to the PFC, yet the relative amount of this receptor is significantly lower than its counterpart²⁶. Early studies indicated that D₁ was most abundant in superficial layers I, II, and III, with slightly lower levels in layers V and VI in primates, while showing specificity to deeper layers in a rat model^{28, 30}. D₂ receptors show laminar localization primarily to layer V. Findings by Richfield et al. suggest a uniform distribution of D₁ receptors across all lamina in cats and monkeys, but rats had increased D₁ receptor binding in deep layers V and VI²⁶. An mRNA expression study of all five receptor subtypes in the PFC of primates found that expression for all five subtypes was highest in layer V³². This was in agreement with studies of mRNA

levels performed in the human PFC³³, suggesting that layer V has a particularly important role in catecholamine activity in the prefrontal cortex.

Norepinephrine acts on two classes of receptors, both α - and β -adrenergic receptors. These two classes are further broken into α_1 and α_2 as well as β_1 , β_2 , and β_3 subtypes. The α subtypes are each further divided into three subclasses, A, B and C³¹. The β -receptors activate adenylate cyclase³⁴, while α_2 -receptors act to inhibit this enzyme^{35, 36}. The α_1 -receptors are linked to PKC and the release of intracellular calcium through G_q coupling^{35, 37}. The β receptors appear less abundant in the PFC than the α receptors and show an inverse laminar distribution²⁸. The α_1 -receptors are more abundant than β -receptors, yet remain less prominent in the PFC than α_2 -receptors. Prazosin, a selective ligand for α_1 -receptors, exhibits strong binding in deep layers V and VI. The most abundant NE receptor in the PFC is the α_2 -receptor. Clonidine binding (α_2) shows a decreasing gradient from superficial to deep layers²⁸. Both α_{2A} and α_{2C} -receptors are found both presynaptically and postsynaptically in the PFC³⁸. Presynaptic autoreceptors provide feedback inhibition to the NE terminal^{38, 39}.

It is at the level of receptor binding that it first becomes apparent that interactions between DA and NE systems are likely to occur. It has been shown that DA is capable of acting as an agonist at adrenergic receptors^{40, 41}. Likewise, D₁ and D₂ radioligands have been shown to be displaced by both DA and NE, implying NE binding to DA receptors⁴². Cornil et al showed that DA has affinity for the α_{2C} -adrenoceptor in rat brain⁴³. It is widely recognized that NE transporters have a higher affinity for DA than for NE, allowing possible interactions through transmitter reuptake. Finally, 2nd generation antipsychotics such as clozapine and olanzapine have affinities for both DA and NE receptors⁴⁴⁻⁴⁶. Due to the possibilities for interactions between these systems, an investigation of the mechanisms of these interactions appears critical to our understanding of the effects of either pathway in PFC function.

DOPAMINE AND NOREPINEPHRINE IN THE PREFRONTAL CORTEX

The importance of interactions between NE and DA is underlined by the roles of these transmitters during PFC function. The prefrontal cortex is thought to control such executive cognitive functions as working memory and attention. Given the innervation patterns of both dopamine and norepinephrine, it is not surprising that both have individually been shown to have links to these functions. Through the use of lesion studies within the prefrontal cortex, as well as studies of structures projecting to the PFC, transmitter

loss-of-function has been explored.

Lesion of DA in the PFC can be performed directly by injection of 6-hydroxydopamine (6-OHDA) into the PFC⁴⁷, or indirectly by injection of 6-OHDA into the VTA which supplies DA to the PFC⁴⁸ along with a NET blocker such as desipramine to spare NE terminals. Studies using both methods have suggested the importance of DA in working memory, and attention⁴⁹. Interestingly, further research has shown that excess DA in the PFC can have detrimental effects on cognitive tasks as well⁵.

Through injection of the NE terminal specific toxin DBH-saporin, similar PFC specific lesions of NE can be performed⁵⁰. Before the development of this toxin, DNAB lesions using 6-OHDA were used¹. Studies using both of these methods have shown cognitive deficits similar to those seen in the DA system^{1, 14, 50}. Once again, excess levels of NE can have detrimental effects^{37, 51}. These studies suggest that there is an optimal range for DA and NE within the PFC necessary for higher order functioning. Given the involvement of the prefrontal cortex in cognitive functions such as working memory, and attention, as well as the role of DA and NE in these processes, understanding the interactions between these transmitters within the PFC could lead to major changes in the treatment of neurological disorders, such as attention-deficit hyperactivity disorder (ADHD) and schizophrenia.

PREVIOUS HYPOTHESES

Past research often cites potential DA/NE interactions as having an effect on their studies' results^{3, 52, 53}. Previous work in this area has focused on drugs that interact with both systems, rather than these systems' interactions with each other, and the body of literature working directly to determine the mechanisms of these interactions is small. It has been well documented that changes in dopamine and norepinephrine in the prefrontal cortex are well-correlated, changing together in disorders such as schizophrenia⁵³, and as a response to physiological changes, such as stress⁵¹. (The link to stress may prove to be of further interest, as stress often induces schizophrenia symptoms. However, this link will not be discussed in this review). The correlation between DA and NE levels in the PFC is particularly evident in response to antipsychotic drugs^{54, 55}. However, the mechanism of this DA/NE interaction is still being debated. Hypotheses that have been put forth include: a direct effect of NE on DA release^{56, 57}, an effect of NE on DA reuptake^{58, 59}, and co-release of DA and NE from NE terminals⁶⁰. Few researchers have actively attempted to validate these hypotheses by studying the mechanisms by which these two transmitters are interacting.

STUDIES ADDRESSING THE DIRECT EFFECT OF NE ON DA RELEASE

Pozzi et al. used lesion studies, along with selective DA and NE reuptake inhibitors, to further the hypothesis that increases in NE directly increase DA levels⁵⁷. This study showed that increasing extracellular NE was correlated to increases in extracellular DA. Similarly, Gresch et al. suggested two possible explanations for their findings, 1) NE regulation of DA through receptors regulating DA release, or 2) transport of DA into noradrenergic terminals⁵⁶.

STUDIES ADDRESSING DA REUPTAKE THROUGH NE TERMINALS

The idea of NE affecting the uptake of DA has been suggested given the relatively low abundance of DA transporter (DAT)⁶¹ in the PFC, and the broad coverage of NE transporter (NET) in this area⁶². Moron et al. were able to show that DAT knockout mice had normal rates of DA uptake in the frontal cortex, while NET knockout mice exhibited greater than 50% loss of DA uptake⁵⁹. This indicates that DA uptake in the PFC occurs largely through NET activity. If NE release increases, the probability of DA being taken up by these transporters decreases, thereby increasing the extracellular levels of DA in the region. In this indirect way, NE may increase extracellular DA. Studies using the α_2 -receptor antagonist mianserin, along with two NET inhibitors, reboxetine and desipramine, suggest that NET uptake of DA is significantly higher in the PFC than in the parietal cortex or occipital cortex⁵⁸ due to a lower NE/DA ratio than in the latter two areas. It is important to note that mianserin was administered via i.p. injection, so effects were global and not PFC specific. Treatment caused an increase in DA levels in all three regions, and the authors attributed this to the effect of the drug in the VTA causing DA neuron firing, rather than action in the PFC. NET's high affinity for DA could cause more rapid clearance of DA than NE, and could cause the increases in DA when extracellular NE is increased. Later research in which mianserin was administered locally suggests that α_2 -receptors have a significant effect locally on DA release in the PFC⁶³.

STUDIES ADDRESSING DOPAMINE AND NOREPINEPHRINE CO-RELEASE

Ahn and Klinman reported on the rate limiting steps of norepinephrine synthesis over 20 years ago⁶⁴. They report that dopamine beta monooxygenase (dopamine beta hydroxylase, DBH), and not tyrosine hydroxylase, may be the rate-limiting step in NE synthesis. DBH is the final enzyme that converts DA into NE within the vesicles of NE terminals. If DBH

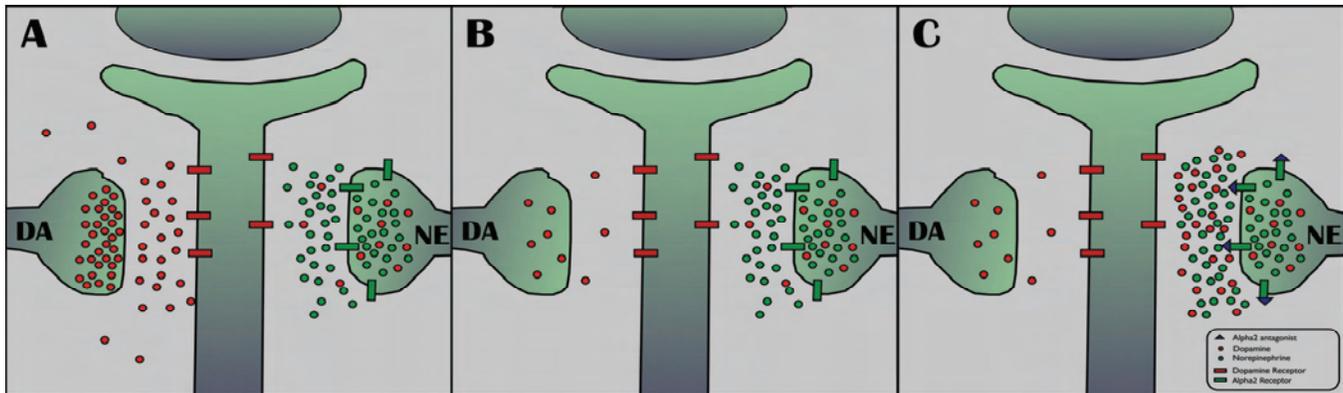


Figure 1 | **A possible mechanism for the effects of olanzapine and clozapine on DA tone** A) Proper DA and NE signaling. B) DA tone disturbance while NE signaling remains intact. C) The effects of a α_2 -receptor antagonist as it re-establishes DA tone through the NE terminal. DA (red circles) and receptors (red boxes), NE (green circles) and α_2 -receptors (green boxes), α_2 -receptor antagonist (blue triangle).

is rate limiting, at times the firing rate of NE neurons could be intensified, causing release of DA from these terminals along with NE. This interaction, coined the “co-release” hypothesis, proposes that DA and NE are released together from the NE terminal⁶⁰. Microdialysis allowed investigation of the possible co-release of DA and NE in the PFC⁶⁰. Looking at DA innervated regions (PFC) and non-, or minutely DA innervated regions (occipital cortex, primary motor cortex) using dialysis, Devoto et al. showed that the extracellular levels of DA were similar in both DA innervated and non-innervated regions. This implies another source of DA in these areas. Using selective α_2 -receptor antagonist infused through the probe, investigators saw increases in DA in all three areas, suggesting that DA was being released through NE terminals, and furthermore that this release was, in part, regulated by α_2 -receptors⁶⁵. The α_2 -receptor agonist, clonidine, reduced extracellular DA levels along with NE levels, while the antagonist, idazoxan, increased DA and NE levels. A further study in 2003 by the same group performed a similar study looking at the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC)⁶⁶. This study further verified that DA is likely being released from both DA and NE terminals in the PFC, but only by DA terminals in subcortical regions. Using clozapine, the first atypical antipsychotic, Devoto et al. showed the effects of this drug on PFC DA and NE levels. In this study, treatment with clozapine elevated both NE and DA levels in the PFC and occipital cortex, as did treatment with a α_2 antagonist. Interestingly, treatment with clonidine, an α_2 -receptor agonist, reversed these effects, while treatment with a D_2 agonist, which has been shown to decrease DA release in the striatum, had no effect⁶⁶. This evidence again suggests that DA is being released through the NE terminal, and that the atypical antipsychotic drug clozapine is acting through a α_2 -receptor mechanism to restore PFC DA levels. In later experiments,

Devoto et al showed that activation of the LC was sufficient to increase extracellular dopamine in the PFC⁶⁷. Considered with the results discussed above, it is likely that this increase is not solely due to the LC acting on the VTA but also through NE terminal firing in the PFC. Finally, Devoto et al. demonstrated that lesioning the VTA and removing DA innervation to the PFC has no effect on extracellular DA levels⁶⁸. Tissue content of DA was significantly reduced, however extracellular levels remained unchanged. These data provide very strong evidence suggesting that NE terminals do, in fact, release DA, providing an alternative explanation to the hypotheses that NE is affecting DA levels through direct interaction with DA terminals or through DA reuptake.

The release of DA from NE terminals may help to explain data derived in our own lab. We have shown that a loss of DA innervation from the VTA causes a loss of dendritic spines on PFC layer V pyramidal cells⁴⁸. This loss of dendritic spines could be related to the loss of cortical volume seen in schizophrenia patients⁶⁹, providing a possible pathological correlate to behavioral data suggesting impaired cognitive function in animals with a loss of PFC DA signaling. Interestingly, the loss of spines in these cells could be reversed through treatment with olanzapine, but not haloperidol. Given the ability of atypical, but not typical antipsychotic drugs to help in the relief of cognitive symptoms of schizophrenia, this lends credibility to the importance of dendritic spines in PFC function. Dendritic structure is maintained through DA tone in the striatum⁷⁰. If the same is true for the PFC, it can be hypothesized that following DA depletion of the PFC, atypical drug treatment acts to restore DA tone through an alternative DA source. Under normal conditions, it appears that extracellular DA comes both from the DA and NE terminals, with DA terminals shouldering the majority of this load (**Figure 1a**). However, in certain states such as schizophrenia, these DA levels are reduced, possibly

through reduced transmission through the DA terminals (**Figure 1b**). Through treatments capable of antagonizing the α_2 -receptor, DA tone can be restored through release of DA through the NE terminal (**Figure 1c**). Clozapine, the original atypical antipsychotic, as well as olanzapine, has a high affinity for α_2 -receptors⁴⁴ making these drugs candidates to act at the NE terminal.

CONCLUSIONS

Atypical antipsychotic drugs appear to have effects on cognitive deficits not seen with typical antipsychotic treatments¹⁸. These drugs also have a restorative effect on DA denervated pyramidal cell morphology in the PFC⁴⁸. Linking these two functions of atypical antipsychotics could provide strong evidence that the ability of atypical antipsychotic drugs to treat the cognitive deficits and negative symptoms of schizophrenia is a result of their ability to affect non-DA receptors, including the α_2 -receptor. Data from Devoto et al. have suggested that atypical antipsychotic drugs are capable of causing release of DA from NE terminals⁶⁶. Our own work suggests that this may be a factor in restoring dendritic spines in the PFC. Further research is critical to linking the interactions of the DA and NE systems to the restorative effects of atypical antipsychotic treatment. In the future, understanding the mechanism of interaction of DA and NE should lead to improved treatments of disorders of the prefrontal cortex, ranging from affective disorders to schizophrenia.

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Shows through lesion studies that co-release of DA is occurring through NE terminals.

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FURTHER INFORMATION

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